

Applicants : Alexander Gad and Dora Lees
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In the Claims

Please amend the claims by replacing all prior versions, and listings, of claims pursuant to 37 C.F.R. §1.121(c) as follows:

1-122. (Canceled)

123. (Currently Amended) In a process for obtaining a pharmaceutical product containing ~~an aqueous~~ a mixture of polypeptides, each of which consists essentially of alanine, glutamic acid, tyrosine and lysine, wherein the mixture has ~~a desired average molecular weight~~ an average molecular weight from 4000 to 13,000 Daltons and in the mixture the molar fraction of alanine is 0.427, of glutamic acid is 0.141, of lysine is 0.337 and of tyrosine is 0.093 and wherein during the process a batch of ~~an aqueous~~ a mixture of polypeptides, each of which consists essentially of alanine, glutamic acid, tyrosine and lysine, is tested using a gel permeation chromatography column to determine whether the mixture has ~~the desired~~ an average molecular weight from 4000 to 13,000 Daltons for inclusion in the pharmaceutical product, the improvement comprising

calibrating the molecular weight obtained using the gel permeation chromatography column by subjecting a plurality of molecular weight markers, each of which is a polypeptide consisting essentially of alanine, glutamic acid, tyrosine and lysine and having a predetermined amino acid sequence, to chromatography on the column to establish a relationship between retention time on the column and molecular weight.

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124-126. (Canceled)

127. (Previously presented) The process of claim 123, wherein the gel permeation chromatography column comprises a cross-linked agarose-based medium, with an exclusion limit of 2×10^6 Daltons, an optimal separation range of 1000 to 3×10^5 Daltons, and a bead diameter of 20-40 μm .

128. (Previously presented) The process of claim 127, wherein the gel permeation chromatography column is Superose 12.

129. (Currently amended) The process of claim 123, wherein in the molecular weight markers the molar fraction of ~~aniline~~ alanine is 0.38 to 0.5, of glutamic acid is 0.13 to 0.15, of tyrosine is 0.08 to 0.10 and of lysine is 0.3 to 0.4.

130. (Currently Amended) The process of claim 129, wherein in the molecular weight markers the molar fraction of ~~aniline~~ alanine is 0.422 to 0.444, of glutamic acid is 0.133 to 0.143, of tyrosine is 0.086 to 0.093 and of lysine is 0.333 to 0.349.

131. (Previously presented) The process of claim 123, wherein one of the molecular weight markers is selected from the group consisting of

AKKYAKKEKAAKKAYKKEAKAKAAEAAAKEAAYEA (SEQ ID NO:1);

AKKYAKKAKAEKAKKAYKAAEAKKAAKYEKAAAEKAAAKEAAYEA (SEQ ID NO:2);

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AKKYAKKEKAYAKKA EKA AAKKAEAKAYKAAEAKKKAEAKYKAEAAKAAAKEAAAYE
A (SEQ ID NO:3);
AKKYAKKEKAYAKAKKAEAKA AAKKAKAEAKKYAKA AKA EKKEYAAAAEAKYKAEAA
KAAAKEAAAYEA (SEQ ID NO:4);
AKKYAKKEKAYAKKA EKA AAKKAEAKAYKAAEAKKKAKAEAKKYAKA AKA EKKEYA
AAEAKYKAEAAKAAAKEAAAYEA (SEQ ID NO:5);
AKKYAKKEKAYAKKA EKA AAKKAEAKAYKAAEAKKKAKAEAKKYAKA AKA EKKEYA
AAEAKYKAEAAKAYKAEAAKAAAKEAAAYEA (SEQ ID NO:6); and
AKKYAKKA EKAYAKKAKAAKEKKAYAKKEAKAYKAAEAKKKAKAEAKKYAKEAAK
AKKEAYKAEAKKYAKA AKA EKKEYAAAAEAKKAEAAKAYKAEAAKAAAKEAAAYEA
(SEQ ID NO:7),

wherein A represents alanine, K represents lysine, Y
represents tyrosine, and E represents glutamic acid.

132. (Previously presented) The process of claim 123,
wherein the plurality of molecular weight markers is

AKKYAKKEKA AAKKAYKKEAKAKAAEAAAKEAAAYEA (SEQ ID NO:1);
AKKYAKKAKAEKAKKAYKAAEAKKAAKYEKAAAEKAAAKEAAAYEA (SEQ ID
NO:2);
AKKYAKKEKAYAKKA EKA AAKKAEAKAYKAAEAKKKAEAKYKAEAAKAAAKEAAAYE
A (SEQ ID NO:3);
AKKYAKKEKAYAKAKKAEAKA AAKKAKAEAKKYAKA AKA EKKEYAAAAEAKYKAEAA
KAAAKEAAAYEA (SEQ ID NO:4);
AKKYAKKEKAYAKKA EKA AAKKAEAKAYKAAEAKKKAKAEAKKYAKA AKA EKKEYA
AAEAKYKAEAAKAAAKEAAAYEA (SEQ ID NO:5);
AKKYAKKEKAYAKKA EKA AAKKAEAKAYKAAEAKKKAKAEAKKYAKA AKA EKKEYA
AAEAKYKAEAAKAYKAEAAKAAAKEAAAYEA (SEQ ID NO:6); and
AKKYAKKA EKAYAKKAKAAKEKKAYAKKEAKAYKAAEAKKKAKAEAKKYAKEAAK
AKKEAYKAEAKKYAKA AKA EKKEYAAAAEAKKAEAAKAYKAEAAKAAAKEAAAYEA
(SEQ ID NO:7),

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wherein A represents alanine, K represents lysine, Y represents tyrosine, and E represents glutamic acid.

133. (Currently Amended) The process of claim 124 123, ~~further comprising a step of lyophilizing of the glatiramer acetate~~ wherein the pharmaceutical product is lyophilized.

134. (Currently Amended) A process for obtaining a pharmaceutical ~~composition~~ product containing an ~~aqueous~~ a mixture of polypeptides, each of which consists essentially of alanine, glutamic acid, tyrosine and lysine, wherein the mixture has ~~a desired average molecular weight~~ an average molecular weight from 4000 to 13,000 Daltons and in the mixture the molar fraction of alanine is 0.427, of glutamic acid is 0.141, of lysine is 0.337 and of tyrosine is 0.093, which comprises obtaining a batch of ~~an aqueous a~~ mixture of polypeptides, each of which consists essentially of alanine, glutamic acid, tyrosine and lysine;

determining the average molecular weight of the mixture of polypeptides in the batch using a molecular weight-calibrated gel permeation chromatography column; and

including in the pharmaceutical product the mixture if the mixture is determined to have ~~the desired~~ an average molecular weight from 4000 to 13,000 Daltons,

~~wherein the calibration of the molecular weight obtained using~~ the gel permeation chromatography column

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is calibrated by ~~comprises~~ subjecting a plurality of molecular weight markers to chromatography on the column to establish a relationship between the retention time on the column and molecular weight, wherein each of the markers is a polypeptide consisting essentially of alanine, glutamic acid, tyrosine and lysine and has a predetermined amino sequence.

135-137. (Canceled)

138. (Previously presented) The process of claim 134, wherein the gel permeation chromatography column comprises a cross-linked agarose-based medium, with an exclusion limit of 2×10^6 Daltons, an optimal separation range of 1000 to 3×10^5 Daltons, and a bead diameter of 20-40 μm .

139. (Previously presented) The process of claim 138, wherein the gel permeation chromatography column is Superose 12.

140. (Currently Amended) The process of claim 134, wherein in the molecular weight markers the molar fraction of ~~alanine~~ alanine is 0.38 to 0.5, of glutamic acid is 0.13 to 0.15, of tyrosine is 0.08 to 0.10 and of lysine is 0.3 to 0.4.

141. (Currently Amended) The process of claim 140, wherein in the molecular weight markers the molar fraction of ~~alanine~~ alanine is 0.422 to 0.444, of glutamic acid is 0.133 to 0.143, of tyrosine is 0.086 to 0.093 and of lysine is 0.333 to 0.349.

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142. (Previously presented) The process of claim 134, wherein one of the molecular weight markers is selected from the group consisting of

AKKYAKKEKAACKKAYKKEAKAKAAEAAAKEAAYEA (SEQ ID NO:1);
AKKYAKKAKAEKAKKAYKAAEAKKAAYEKAAAEEKAAAKEAAYEA (SEQ ID NO:2);
AKKYAKKEKAYAKKAKEKAACKKAEAKAYKAAEAKKKAEAKYKAEAAKAAAKEAAYEA (SEQ ID NO:3);
AKKYAKKEKAYAKKAKEKAACKKAEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA AAEEAKYKAEAA KAAAKEAAYEA (SEQ ID NO:4);
AKKYAKKEKAYAKKAKEKAACKKAEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA AAEEAKYKAEAAKAAAKEAAYEA (SEQ ID NO:5);
AKKYAKKEKAYAKKAKEKAACKKAEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA AAEEAKYKAEAAKAYKAEAAKAAAKEAAYEA (SEQ ID NO:6); and
AKKYAKKAEKAYAKKAKAAKEKKAYAKKEAKAYKAAEAKKKAKAEAKKYAKEAAK AKKEAYKAEAKKYAKAAKAEKKEYA AAEEAKKAEAAKAYKAEAAKAAAKEAAYEA (SEQ ID NO:7),

wherein A represents alanine, K represents lysine, Y represents tyrosine, and E represents glutamic acid.

143. (Previously presented) The process of claim 134, wherein the plurality of molecular weight markers is

AKKYAKKEKAACKKAYKKEAKAKAAEAAAKEAAYEA (SEQ ID NO:1);
AKKYAKKAKAEKAKKAYKAAEAKKAAYEKAAAEEKAAAKEAAYEA (SEQ ID NO:2);
AKKYAKKEKAYAKKAKEKAACKKAEAKAYKAAEAKKKAEAKYKAEAAKAAAKEAAYEA (SEQ ID NO:3);

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AKKYAKKEKAYAKAKKAEAKAAKKAKAEAKKYAKAAKAEKKEYAAAAEAKYKAEAA
KAAAKEAAAYEA (SEQ ID NO:4);
AKKYAKKEKAYAKKAEKAAKKAEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA
AAEAKYKAEAAKAAAKEAAAYEA (SEQ ID NO:5);
AKKYAKKEKAYAKKAEKAAKKAEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA
AAEAKYKAEAAKKAYKAEAAKAAAKEAAAYEA (SEQ ID NO:6); and
AKKYAKKAEKAYAKKAKAAKEKKAYAKKEAKAYKAAEAKKKAKAEAKKYAKEAAK
AKKEAYKAEAKKYAKAAKAEKKEYAAAAEAKKAEAAKAYKAEAAKAAAKEAAAYEA
(SEQ ID NO:7),

wherein A represents alanine, K represents lysine, Y represents tyrosine, and E represents glutamic acid.

144. (Currently Amended) The process of claim ~~135~~ 134, further comprising a step of lyophilizing ~~of~~ the ~~glatiramer acetate mixture~~ mixture having the ~~desired~~ average molecular weight ~~distribution~~ from 4000 to 13,000 Daltons.

145. (Currently Amended) A process for determining the average molecular weight of an aqueous mixture of polypeptides, each of which consists essentially of alanine, glutamic acid, tyrosine and lysine, wherein in the mixture the molar fraction of alanine is 0.427, of glutamic acid is 0.141, of lysine is 0.337 and of tyrosine is 0.093, which comprises subjecting the mixture to chromatography on a molecular weight-calibrated gel permeation chromatography column so as to determine the average molecular weight of the mixture, ~~wherein the calibration of the molecular weight obtained using the gel permeation chromatography column is calibrated by~~ comprises subjecting a

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plurality of molecular weight markers to chromatography on the column to establish a relationship between retention time on the column and molecular weight, wherein each of the markers is a polypeptide consisting essentially of alanine, glutamic acid, tyrosine and lysine and has a predetermined amino acid sequence.

146-148. (Canceled)

149. (Previously presented) The process of claim 145, wherein the gel permeation chromatography column comprises a cross-linked agarose-based medium, with an exclusion limit of 2×10^6 Daltons, an optimal separation range of 1000 to 3×10^5 Daltons, and a bead diameter of 20-40 μm .

150. (Previously presented) The process of claim 149, wherein the gel permeation chromatography column is Superose 12.

151. (Currently Amended) The process of claim 145, wherein in the molecular weight markers the molar fraction of ~~aniline~~ alanine is 0.38 to 0.5, of glutamic acid is 0.13 to 0.15, of tyrosine is 0.08 to 0.10 and of lysine is 0.3 to 0.4.

152. (Currently Amended) The process of claim 151, wherein in the molecular weight markers the molar fraction of ~~aniline~~ alanine is 0.422 to 0.444, of glutamic acid is 0.133 to 0.143, of tyrosine is 0.086 to 0.093 and of lysine is 0.333 to 0.349.

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153. (Previously presented) The process of claim 145, wherein one of the molecular weight markers is selected from the group consisting of

AKKYAKKEKAAKKAYKKEAKAKAAEAAAKEAAYEA (SEQ ID NO:1);
AKKYAKKAKAEKAKKAYKAAEAKKAAKYEKAAAEKAAAKEAAYEA (SEQ ID NO:2);
AKKYAKKEKAYAKKAEKAAKKAEAKAYKAAEAKKKAEAKYKAEAAKAAAKEAAYEA (SEQ ID NO:3);
AKKYAKKEKAYAKAKKAEAKAAKKAKAEAKKYAKAAKAEKKEYAAAAEAKYKAEAAKAAAKEAAYEA (SEQ ID NO:4);
AKKYAKKEKAYAKKAEKAAKKAEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA AAEAKYKAEAAKAAAKEAAYEA (SEQ ID NO:5);
AKKYAKKEKAYAKKAEKAAKKAEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA AAEAKYKAEAAKKAYKAEAAKAAAKEAAYEA (SEQ ID NO:6); and
AKKYAKKAEKAYAKKAKAAKEKKAYAKKEAKAYKAAEAKKKAKAEAKKYAKEAAK AKKEAYKAEAKKYAKAAKAEKKEYAAAAEAKKAEAAKAYKAEAAKAAAKEAAYEA (SEQ ID NO:7),

wherein A represents alanine, K represents lysine, Y represents tyrosine, and E represents glutamic acid.

154. (Previously presented) The process of claim 145, wherein the plurality of molecular weight markers is

AKKYAKKEKAAKKAYKKEAKAKAAEAAAKEAAYEA (SEQ ID NO:1);
AKKYAKKAKAEKAKKAYKAAEAKKAAKYEKAAAEKAAAKEAAYEA (SEQ ID NO:2);
AKKYAKKEKAYAKKAEKAAKKAEAKAYKAAEAKKKAEAKYKAEAAKAAAKEAAYEA (SEQ ID NO:3);
AKKYAKKEKAYAKAKKAEAKAAKKAKAEAKKYAKAAKAEKKEYAAAAEAKYKAEAAKAAAKEAAYEA (SEQ ID NO:4);

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AKKYAKKEKAYAKKA EKA AAKKAEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA
AAEAKYKAEAAKAAAKEAAAYEA (SEQ ID NO:5);
AKKYAKKEKAYAKKA EKA AAKKAEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA
AAEAKYKAEAAKKAYKAEAAKAAAKEAAAYEA (SEQ ID NO:6); and
AKKYAKKAEKAYAKKAKAAKEKKAYAKKEAKAYKAAEAKKKAKAEAKKYAKEAAK
AKKEAYKAEAKKYAKAAKAEKKEYAAAEAKKAEAAKAYKAEAAKAAAKEAAAYEA
(SEQ ID NO:7),

wherein A represents alanine, K represents lysine, Y represents tyrosine, and E represents glutamic acid.

155. (Currently Amended) A process for determining whether an aqueous mixture of polypeptides, each of which consists essentially of alanine, glutamic acid, tyrosine and lysine, has ~~a desired average molecular weight~~ an average molecular weight from 4000 to 13,000 Daltons, wherein in the mixture the molar fraction of alanine is 0.427, of glutamic acid is 0.141, of lysine is 0.337 and of tyrosine is 0.093, which process comprises subjecting the mixture to a calibrated gel permeation chromatography column to determine the average molecular weight of the mixture and comparing the average molecular weight so determined to the desired average molecular weight, wherein the calibration of the molecular weight obtained using the gel permeation chromatography column is calibrated by ~~comprises~~ subjecting a plurality of molecular weight markers to chromatography on the column to establish a relationship between retention time on the column and molecular weight, wherein each of the markers is a polypeptide consisting essentially of alanine, glutamic

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acid, tyrosine and lysine and has a predetermined amino acid sequence.

156-158. (Canceled)

159. (Previously presented) The process of claim 155, wherein the gel permeation chromatography column comprises a cross-linked agarose-based medium, with an exclusion limit of 2×10^6 Daltons, an optimal separation range of 1000 to 3×10^5 Daltons, and a bead diameter of 20-40 μm .

160. (Previously presented) The process of claim 159, wherein the gel permeation chromatography column is Superose 12.

161. (Currently amended) The process of claim 155, wherein in the molecular weight markers the molar fraction of ~~aniline~~ alanine is 0.38 to 0.5, of glutamic acid is 0.13 to 0.15, of tyrosine is 0.08 to 0.10 and of lysine is 0.3 to 0.4.

162. (Currently amended) The process of claim 161, wherein in the molecular weight markers the molar fraction of ~~aniline~~ alanine is 0.422 to 0.444, of glutamic acid is 0.133 to 0.143, of tyrosine is 0.086 to 0.093 and of lysine is 0.333 to 0.349.

163. (Previously presented) The process of claim 155, wherein one of the molecular weight markers is selected from the group consisting of

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AKKYAKKEKAAKKAYKKEAKAKAAEAAAKEAAAYEA (SEQ ID NO:1);
AKKYAKKAKAEKAKKAYKAAEAKKAAKYEKAAAEKAAAKEAAAYEA (SEQ ID
NO:2);
AKKYAKKEKAYAKKAKEKAACKKAEAKAYKAAEAKKKAEAKYKAEAAKAAAKEAAAYE
A (SEQ ID NO:3);
AKKYAKKEKAYAKAKKAEAKAAKKAKAEAKKYAKAAKAEKKEYAAAEAKYKAEAA
KAAAKEAAAYEA (SEQ ID NO:4);
AKKYAKKEKAYAKKAKEKAACKKAEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA
AAEAKYKAEAAKAAAKEAAAYEA (SEQ ID NO:5);
AKKYAKKEKAYAKKAKEKAACKKAEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA
AAEAKYKAEAAKKAYKAEAAKAAAKEAAAYEA (SEQ ID NO:6); and
AKKYAKKAEKAYAKKAKAAKEKKAYAKKEAKAYKAAEAKKKAKAEAKKYAKEAAK
AKKEAYKAEAKKYAKAAKAEKKEYAAAEAKKAEAAKAYKAEAAKAAAKEAAAYEA
(SEQ ID NO:7),

wherein A represents alanine, K represents lysine, Y
represents tyrosine, and E represents glutamic acid.

164. (Previously presented) The process of claim 155,
wherein the plurality of molecular weight markers is

AKKYAKKEKAAKKAYKKEAKAKAAEAAAKEAAAYEA (SEQ ID NO:1);
AKKYAKKAKAEKAKKAYKAAEAKKAAKYEKAAAEKAAAKEAAAYEA (SEQ ID
NO:2);
AKKYAKKEKAYAKKAKEKAACKKAEAKAYKAAEAKKKAEAKYKAEAAKAAAKEAAAYE
A (SEQ ID NO:3);
AKKYAKKEKAYAKAKKAEAKAAKKAKAEAKKYAKAAKAEKKEYAAAEAKYKAEAA
KAAAKEAAAYEA (SEQ ID NO:4);
AKKYAKKEKAYAKKAKEKAACKKAEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA
AAEAKYKAEAAKAAAKEAAAYEA (SEQ ID NO:5);
AKKYAKKEKAYAKKAKEKAACKKAEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA
AAEAKYKAEAAKKAYKAEAAKAAAKEAAAYEA (SEQ ID NO:6); and

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AKKYAKKAEKAYAKKAKAAKEKKAYAKKEAKAYKAAEAKKKAKAEAKKYAKEAAK
AKKEAYKAEAKKYAKAAKAEKKEYAAAEAKKAEAAKAYKAEAAKAAAKEAAYEA
(SEQ ID NO:7),

wherein A represents alanine, K represents lysine, Y
represents tyrosine, and E represents glutamic acid.